REMARKS

Claims 1, 2 , 4, 8, 9, 11, and 12 are still pending. Applicants have amended Claims 1, 2, and 4. Applicants have amended Claims 1-2 to recite the amino acid receptor being metabotropic glutamate as described in the specification on, for example, page 21, lines 13-21. Applicants have amended Claim 4 as suggested by the Examiner to define metabotropic glutamate disease conditions, as described in the specification on, for example page 16, lines 29- page 17, line 7 and page 17, line 18. Lastly, Applicants have canceled Claim 11. Thus, the changes are supported by the specification and are not new matter.

Definiteness:

"metabotropic glutamate disease conditions"

The Examiner rejected Claim 4 as allegedly indefinite because the phrase "metabotropic glutamate disease conditions" is allegedly uncertain.

The Examiner suggested "A method for treating a disease condition which is treatable by modulation of the activity of metabotropic glutamate receptors, said method comprising: administering to a patient having said disease condition, a therapeutically effective amount which is sufficient to modulate the activity of metabotropic glutamate receptors..."

To facilitate prosecution, Applicants have amended Claim 4, as the Examiner suggested. However, Applicants note that the phrase "metabotropic glutamate disease conditions" is not indefinite because the specification defines metabotropic glutamate receptors in detail on, for example, page 16, lines 29 – page 17 line 7 and also defines diseases contemplated for treatment on, for example, page 17, line 18- 27. Thus, the specification defines "metabotropic glutamate disease conditions" as such diseases involving metabotropic glutamate.

"excitatory amino acid receptor"

The Examiner alleged an insufficient antecedent basis for "excitatory amino acid receptor" in Claim 1. Applicants have amended Claim 1 by replacing "said excitatory amino acid receptor" with "said metabotropic glutamate receptors." To facilitate prosecution,

Applicants have also amended Claim 2 to replace "said excitatory amino acid receptor" with "said metabotropic glutamate receptor."

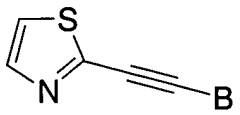
Novelty:

The Examiner rejected Claims 1, 2, 4, and 9-11 under 35 U.S.C. 102(b) as allegedly anticipated by WO 96/33181 ('181) because the '181 reference allegedly teaches an ethynylthiazole derivative, and salt thereof, and a method of treating and preventing various diseases, including angina pectoris (Pgs. 37-40, 62-68, Claims 1-22).

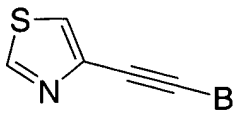
Claims 1, 2, 4, and 9-10 are *methods*, not *compositions*, of using alkynylene thiazole for *modulating the activity of metabotropic glutamate receptors* or treating *pain.*

In contrast, the '181 reference does not disclose *methods* of using alkynylene thiazoles to modulate the activity of metabotropic glutamate receptors or treat pain. The '181 reference restrictively discloses *methods* of using certain *2-* ethynylthiazoles only as allergenic disease treating agents and leukotrine antagonists (p. 37 and Claims 21-22), not as *modulating the activity of metabotropic glutamate receptors* or treating *pain.*

Furthermore, the '181 reference restrictively discloses only certain *ethynyl*thiazoles where only *ethynyl* joins a thiazolyl to an aryl, the aryl is linked to another extensive moiety, **A-$(CH_2)_m$-G**, and the *ethynyl*thiazole must be *2-ethynyl*thiazoles, as in:



In other words, the '181 reference only discloses *2-ethynyl*thiazoles where ethynyl joins a thiazolyl at a site adjacent to a S and N atom. The '181 reference does not disclose *alkynylene* thiazoles where any *alkynylene* joins a thiazolyl at a site adjacent to a N and C atom, such *as 4-alkynyl* thiazoles:



Consequently, the '181 reference does not anticipate the method Claims 1, 2, 4, and 9-10 because the '181 reference does not disclose methods of modulating the activity of metabotropic glutamate receptors or treating pain. Nor does the '181 reference anticipate composition Claim 11 because the '181 reference does not disclose *alkynylene* thiazoles where any *alkynylene* joins a thiazolyl at a site adjacent to a N and C atom, such as ***4-alkynyl*** thiazoles.

Lack of Obviousness:

The Examiner alternatively rejected Claims 1, 2, 4, 9, and 11 as allegedly obvious over the '181 reference because the '181 reference allegedly suggests that toluene sulfonic salt of the claimed compounds as pharmaceutically acceptable salts are well known in the art, even though the Examiner admitted that the '181 reference does not expressly disclose a toluene sulfonic salt of the claimed compounds.

As discussed earlier, Claims 1, 2, 4, and 9-10 are *methods*, not *compositions*, of using alkynylene thiazole for *modulating the activity of metabotropic glutamate receptors* or treating *pain*.

In contrast, the '181 reference, as discussed earlier, does not suggest *methods* of using alkynylene thiazoles to *modulate the activity of metabotropic glutamate receptors or treat pain*. The '181 reference restrictively discloses *methods* of using certain 2- ethynylthiazoles only as allergenic disease treating agents and leukotrine antagonist, not as *modulating the activity of metabotropic glutamate receptors* or treating *pain*. Furthermore, the '181 reference, as discussed earlier, only discloses ***2-ethynyl***thiazoles where ethynyl joins a thiazolyl at a site adjacent to a S and N atom. The '181 reference does not disclose *alkynylene* thiazoles where any *alkynylene* joins a thiazolyl at a site adjacent to a N and C atom, such as ***4-alkynyl*** thiazoles.

Consequently, to demonstrate a prima facie case of obviousness, the Examiner must prove: 1) some suggestion or motivation either in the '181 reference or in the knowledge generally available to one of ordinary skill in the art to modify the '181 reference or combine the teachings of the reference; 2) a reasonable expectation of success; and 3) the prior art reference (or references when combined) teaches or suggests all the claim limitations. MPEP 2143.

In Applicants' case, the Examiner merely alleged that one of ordinary skill in the art would have been motivated to use any of a number of salts, including toluene sulfonic salt, with the expectation that the salts would be pharmaceutically acceptable without demonstrating a motivation to modify or demonstrating a reasonable expectation of success.

Regarding modifying, the Examiner did not demonstrate a motivation to modify the '181 reference by using the restrictively disclosed 2-ethynylthiazoles to modulate the activity of metabotropic glutamate receptors or treat pain, particularly when the '181 reference does not suggest that these restrictively disclosed 2-ethynylthiazoles are suitable for such a purpose. Just because the restrictively disclosed 2-ethynylthiazoles might be used as allergenic disease treating agents and leukotrine antagonists does not motivate nor suggest that the 2-ethynylthiazoles would be suitable for treating any other medical condition, such as modulating the activity of metabotropic glutamate receptors or treating pain.

Nor did the Examiner demonstrate a reasonable expectation of success in using these restrictively disclosed 2-ethynylthiazoles to modulate the activity of metabotropic glutamate receptors or treat pain, absent any data to support otherwise.

Furthermore, the Examiner did not demonstrate a motivation to modify the restrictively disclosed *2-ethynyl*thiazoles to *alkynylene* thiazoles where any *alkynylene* joins a thiazolyl at a site adjacent to a N and C atom, such as ***4-alkynyl*** thiazole, instead of a site adjacent to S and N. Nor did the Examiner demonstrate a reasonable expectation of success in making such modifications.

Thus, *method* Claims 1, 2, 4 and 9-10 would not have been obvious to one of ordinary skill in the art in view of the '181 reference because the '181 reference does not describe, suggest or motivate using the restrictively disclosed 2-ethynylthiazoles *to modulate the activity of metabotropic glutamate receptors or treat pain.*

Claim 11 has been cancelled without prejudice. Thus, the rejection under 35 U.S.C. 103 has been completely avoided. Applicants expressly reserve the right to file a divisional application to subject matter of Claim 11.

Applicants respectfully submit that the application is in condition for allowance and request a Notice of Allowance. If a telephone communication with Applicants' Attorney would be of assistance in handling this matter, please contact the undersigned attorney. Any fees required in connection with this submission may be taken from Merck Deposit Account No. 13-2755.

Respectfully submitted,

By: David L Rose

David L. Rose
Reg. No. 26,332
Attorney for Applicants

MERCK & CO., Inc.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-4777

Date: November 13, 2002

CLAIMS MARKED-UP TO SHOW CHANGES

The brackets indicate deletion and underlines represent addition.

1. (Amended Fourth) A method of modulating the activity of metabotropic glutamate receptors, said method comprising:

contacting said receptors with at least one compound having the structure **A-L-B** or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, or pharmaceutically acceptable salts thereof, in an amount sufficient to modulate the activity of said [excitatory amino acid receptor] metabotropic glutamate receptors wherein:

A is thiazolyl optionally substituted with 1 or 2 independent halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, heterocycle, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxy, ester, cyano, amine, amide, amidine, amido, sulfonyl or sulfonamide;

L is alkynylene; and

B is substituted or unsubstituted aryl.

2. (Amended Thrice) The method according to claim 1, wherein said [excitatory amino acid] metabotropic glutamate receptor is a Group 1 metabotropic glutamate receptor.

4. (Amended fourth) A method for treating a disease condition which is treatable by modulation of the activity of metabotropic glutamate receptors [metabotropic glutamate disease conditions], said method comprising:

administering to a patient having [a] said disease condition, a therapeutically effective amount which is sufficient to modulate the activity of metabotropic glutamate receptors of at least one compound having the structure **A-L-B** or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, or pharmaceutically acceptable salts thereof, wherein:

A is thiazolyl optionally substituted with 1 or 2 independent halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, heterocycle, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxy, ester, cyano, amine, amide, amidine, amido, sulfonyl or sulfonamide;

L is alkynylene; and

B is substituted or unsubstituted aryl.